SENSORS AND PROBES

Magnetic signaling control

Molecular assemblies on magnetic nanoparticles enable localized activation of signaling pathways inside cells.

Light is a familiar tool for the observation of biological processes and, more recently, for their manipulation. Through the expression of engineered photosensitive proteins in cells, signaling pathways can be controlled with the ease of a light switch.

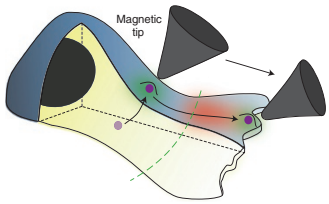
Although light has many advantages for cellular manipulation, it also comes with some drawbacks. Photosensitive proteins respond to a relatively wide portion of the visible light spectrum, which gives rise to problems such as undesired background activation. This has led some scientists to explore other, more targeted tools for remote control.

Magnetic forces are commonly used for imaging and spectroscopy, but recently they have taken the stage as tools for manipulation, too. For the latter, one first needs to load small magnetic nanoparticles (MNPs) into cells. These small particles are attracted by magnetic forces that can be locally exerted.

Researchers can also functionalize MNPs by attaching proteins to them, rendering the proteins susceptible to magnetic forces. Work by Maxime Dahan, at Ecole Normale Supérieure (now at Institut Curie) in Paris, and collaborators shows how this strategy, named 'magnetogenetics', can be used to localize proteins inside cells and control the spatial activation of signaling pathways.

Magnetism was, it turns out, just what Dahan and his colleagues needed to address questions of cell polarity. Cell polarity arises through the localization of specific proteins to specific areas of the cell, particularly at the membrane. But how exactly is polarity established in response to protein activity gradients? How robust is a cell polarity signal? To Dahan, optogenetic approaches were not fully satisfactory to address these questions: he wanted absolute control over a protein's location inside a cell, but light-activated proteins often diffuse away from the site of activation.

To develop the necessary tools, Dahan reached out to collaborators in other areas, such as Jacob Piehler of the University of Osnabrück in Germany, an expert in functionalizing probes for biological investigation. "It turned out to be pretty tricky to manipulate magnetic nanoparticles in the cytoplasm; we realized that no one had attempted to systematically do this before," says Dahan.



Functionalized magnetic particles (purple) are moved around the cell by magnetic forces. Reprinted from *Nature Nanotechnology*.

The team first developed methods to functionalize the MNPs (about 500 nanometers in diameter) with proteins of interest. They synthesized molecular assemblies on the surface of MNPs *in vitro* and then introduced the functionalized particles into cells by microinjection. Alternatively, the team could modify cells to express proteins of interest fused to a HaloTag ligand and microinject HaloTag-functionalized MNPs into the cells.

Once cells were equipped with the MNPs carrying the proteins of interest, the researchers used a sharp magnetic tip to deliver forces that would bring the functionalized MNPs precisely where they wanted them.

Dahan and his colleagues functionalized MNPs with the catalytic domain of TIAM1, a protein that activates the Rho-GTPase Rac1, which in turn induces morphological changes in the cell membrane upon activation. They placed the magnetic tip at different positions in the cell surface, triggering the localized formation of membrane protrusions. To their surprise, they found that Rac1 produced membrane protrusions in a cell context–dependent manner. Continuing to use these tools to unveil the rules behind cell polarity establishment is one of Dahan's priorities.

He is also enthusiastic about the method's potential to control other types of molecules, such as RNA or DNA, whose precise location can be critical for cellular function. The one major drawback of this method is the need to microinject the particles in the first place, but they are already working around this problem.

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RESEARCH PAPERS
Etoc, F. *et al.* Subcellular control of Rac-GTPase signalling by magnetogenetic manipulation inside living cells. *Nat. Nanotechnol.* **8**, 193–198 (2013).